REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 48-59 and 62-68 are in the case.

I. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 54-59 stand provisionally rejected on obviousness-type double patenting grounds as allegedly unpatentable over claims 31, 32 and 38-41 of copending Application Serial No. 09/930,494. Applicants will consider filing a Terminal Disclaimer when otherwise allowable subject matter is indicated.

II. THE OBVIOUSNESS REJECTION

Claims 48-59 and 62-68 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Page et al (1997) in combination with U.S. 6,316,426 to von Borstel et al. This rejection is respectfully traversed.

At the outset, it is noted that the Office continues to assert (page 5 of the action, second complete paragraph) that "applicant has merely found a new property of the instant uridine compounds.... and such a discovery does not constitute a new use." It is well established that patent protection may be secured in the United States for the discovery of a new or non-obvious property of a compound by way of claims directed to a new method of treatment. Thus, the Action's characterization of the present invention as the "mere discovery of a new property" is wrong. As will be clear from the arguments presented below, the present invention as claimed is not rendered obvious by the combined disclosures of Page and von Borstel.

Page uses uridine to treat four patients having a rare disease characterized by excess activity of the enzyme 5'-nucleotidase (an enzyme involved in degradation of nucleotides). In scientific publications describing these patients (*see*: Page, et al., Adv. Exp. Med. Biol. 1998; 431:789-92 and Page et al., Adv. Exp. Med. Biol. 1991;309B:345-8, copies of record), there is no suggestion of mitochondrial respiratory chain dysfunction acting as a molecular basis for cytosolic 5'-nucleotidase excess. The finding by Page that nucleotide precursors (uridine or ribose) are clinically useful in treating a disorder in which the only known molecular deficit is an excess of an enzyme (5'-nucleotidase) involved in nucleotide degradation would **not**, therefore, have led one of ordinary skill to suspect that uridine or ribose would be useful in treating conditions caused by mitochondrial respiratory chain dysfunction, even those which might manifest some similar symptoms.

von Borstel discloses that acylated ribonucleoside derivatives are effective in treating a number of disorders that involve functional impairments in tissue and organ systems involving metabolic deficiencies. Therefore, even if one of ordinary skill would have been motivated to combine Page and von Borstel to treat 5'-nucleotidase excess (it is believed one of ordinary would **not** have been so motivated), one of ordinary skill would still not have arrived at the claimed invention of treating pathophysiological consequences of mitochondrial respiratory chain dysfunction. Accordingly, no *prima facie* case of obviousness has been established in this case.

The Office continues to base its position with respect to unpatentability on the notion that "The population treated by the method of Page is the same or, at the very least, substantially overlaps the population treated by the instant method." (page 5 of

the Action, second complete paragraph). However, the Office has failed to establish that the patient populations truly overlap. Similar and even overlapping symptoms can result from very different causes. Therefore overlapping symptoms are not sufficient to establish a *prima facie* case of obviousness.

As has been demonstrated in the record of this case, unrelated diseases can have overlapping symptoms. It follows, therefore, that the effectiveness of a particular drug in treating a symptom in one disorder does not necessarily, or even generally, imply that the drug will be useful in treating other diseases with similar symptoms. Numerous examples of this have been earlier provided in this case. Thus, for example, epilepsy or related seizure disorders may be caused by tumors, poisons, mitochondrial defects, or simply self-amplifying circuits of neural activity without other organic defects causing the seizures. Seizure episodes in a susceptible person can be triggered by progesterone deficits, e.g. associated with the menstrual cycle. Although the clinical symptoms – seizures – may look similar, the treatments will vary according to the underlying problem. Valproate (Depakote) is a widely-used anti-seizure medication, but it can actually exacerbate seizures (and other manifestations of mitochondrial disease) caused by mitochondrial deficits, due to its inhibitory effect on mitochondrial respiration. For someone with seizures triggered by a progesterone deficit, progesterone or an analog thereof is more appropriate than increased doses of other anti-seizure medications, which have debilitating side effects at higher doses. Some seizure disorders associated with *foci* of hyperexcitable neurons are best treated with electrodes inserted into the brain, which would be inappropriate for seizures caused by

metabolic deficits. Copies of literature references in support of this were submitted with the previous response.

Another example of a condition which can arise from different causes is arthritis. Pain in the joints can be caused by autoimmune attack (rheumatoid arthritis, psoriatic arthritis, or lupus-associated), osteoarthritis, infections, e.g. lime disease, gout, deposition of antibody complexes, etc. All of these disorders may present with joint pain as a predominant symptom, but the appropriate treatments are very different for each of these different diseases that underlie similar symptoms, e.g. anti-TNF therapies for rheumatoid arthritis, B-Cell suppressors for Lupus, nonsteroidal anti-inflammatory drugs for osteoarthritis, antibiotics for Lyme disease, allopurinol for gout. Again, the previous response was accompanied by literature evidence in support of this.

Many other examples are possible in which symptoms themselves provide inadequate information for determining their cause and appropriate treatment. Developmental delays may arise from a variety of underlying causes, including metabolic defects such as phenylketonuria, lead or mercury poisoning, epilepsy, or a variety of genetic defects. A diet low in phenylalanine helps patients with phenylketonuria (in which an enzyme deficiency prevents phenylalanine metabolism), but is useless in other conditions involving developmental delay or seizures. Lead and mercury poisoning can perhaps helped by administration of chelating agents which are useless in diseases not caused by heavy metals. Antiepileptic drugs like valproate or lamictal can help developmental delays secondary to disruptions in brain function caused by seizures, but may be detrimental in disorders not caused by seizures.

The relationship between the molecular anomaly, 5'-nucleotidase excess, and symptoms in the children described by Page et al. is not clear. As the authors point out, the disorder is not associated with actual uridine nucleotide deficits (and the symptoms do not match those of the only known pyrimidine deficit disorder, Orotic Aciduria). Uridine and related pyrimidine compounds were initially tested in these patients because the first one identified presented with megaloblastic anemia (a primary symptom of orotic aciduria), which was later attributed to her anti-seizure medication. The finding that uridine was helpful was actually fortuitous and does not provide a basis for asserting that uridine would be helpful in similar symptoms or symptom complexes associated with other diseases.

In addition, the cited Page et al paper is not the first publication of the use of uridine to treat 5'-nucleotidase excess. This was published earlier in Page, et al., "A Syndrome of Megaloblastic Anemia, Immunodeficiency, and Excessive Nucleotide Degradation," in Purine and Pyrimidine Metabolism in Man VII, Part B, Harkness, et al. eds (1991) pp. 345-348 (of record). The fact that between 1991 and the subject invention no one used uridine compounds to treat pathophysiological consequences of mitochondrial respiratory chain dysfunction is further evidence of its nonobviousness.

Prior to the effective filing date of the subject application, a number of diseases were known to be mitochondrial in origin. Yet they were not treated with pyrimidine nucleotide precursors. This observation refutes the Office's position that it would have been obvious to treat any and all mitochondrial diseases using pyrimidine nucleotide precursors. Further evidence in support of this was presented with the previous response.

In view of the above, it is believed that a *prima facie* case of obviousness has not been generated in this case. Withdrawal of the obviousness rejection is respectfully requested.

Favorable action is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:lfm
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100